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ORIGINAL RESEARCH

Association Between Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) and Short-Term Progression of Carotid Atherosclerosis Among Early Middle Age Adults

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Background: The association between Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) and the development of new carotid plaque in young adults requires further evidence from prospective studies.

Methods: In this study, young adults underwent abdominal and a carotid ultrasounds measurement were included. The carotid plaque progression was assessed in 2 years after baseline. MASLD is defined according to the liver ultrasound findings and self-reported alcohol consumption. Stepped adjusting multivariable logistic regression were employed to analyze the association between MASLD and the outcome. Subgroup analysis was conducted among sex and different amount of metabolic risk factors.

Results: A total of 36.54% (2411/6598) of all participants had MASLD at baseline. Among them, 626 (9.49%) participants were found new onset of carotid plaque in two years. Subjects who had progression of plaque had higher proportion of MASLD (53.99% vs 34.71%, SMD=0.396). Statistically significant positive associations were observed in unadjusted logistic regression models in overall or each sex, respectively. After fully adjustment, the association was only significant among female (OR:2.19, 95% CI: 1.28–3.72) and those had no metabolic risk factor (OR:1.67,95% CI:1.01–2.76). No significant associations were identified in all male subgroups, whereas the associations were still existing among female subgroups.

Conclusion: MASLD was found to be a risk factor of progression of carotid plaque among females and those who had not suffered from metabolic risk factor. Prevention should be focused on young adults who have MASLD at physical examination to reduce their risk of future atherosclerosis.

Keywords: MASLD, atherosclerosis, risk factor

Introduction

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) has become a major public health concern, closely linked to metabolic syndrome and its associated cardiovascular risks.[1] It encompasses a range of liver conditions, from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), and is strongly correlated with obesity, insulin resistance, dyslipidemia, and hypertension. The classification of fatty liver disease has undergone significant revision, moving from the exclusion-based non-alcoholic fatty liver disease (NAFLD) to the affirmative, inclusion-based MASLD. The new definition of MASLD requires hepatic steatosis and at least one cardiometabolic risk factor, while still largely excluding high alcohol consumption and allowing clinicians to better identify patients at higher risk of disease progression and related complications.[2,3] Studies suggested that MASLD may play a key role in accelerating atherosclerosis.[4,5] The prevalence of MASLD is rising globally, affecting approximately 20–30% of the general population,

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with similar trends observed in pediatric and adult populations.[6,7] Management of MASLD is multidisciplinary, with a focus on lifestyle changes and addressing associated conditions. Importantly, MASLD is recognized as a multisystemic disorder, and the leading causes of mortality for these patients are cardiovascular diseases (CVD) and extrahepatic malignancies, rather than liver failure alone. It acts as an independent risk factor for atherosclerosis, coronary artery disease, and chronic kidney disease. Beyond its hepatic implications, MASLD is increasingly recognized as an independent risk factor for CVD, including atherosclerosis, coronary artery disease, and stroke.[8–10]

Carotid atherosclerosis, characterized by increased carotid intima-media thickness (IMT) and the presence of plaques, serves as a reliable marker for subclinical atherosclerosis and predicts future cardiovascular events.[11,12] Studies have demonstrated a strong association between MASLD and carotid atherosclerosis, even in children and young adults, suggesting that MASLD may contribute to early vascular changes.[13,14] For instance, Pacifico et al found that obese children with MASLD exhibited significantly increased carotid IMT compared to their non-MASLD counterparts, independent of traditional cardiovascular risk factors. Similarly, a systematic review demonstrated that MASLD is associated with a 13% increase in carotid IMT and a higher prevalence of carotid plaques in adults.[9] While previous studies have examined the relationship between MASLD and carotid atherosclerosis in both adults and children, there is limited evidence on the short-term progression of carotid plaques in early middle-aged adults with MASLD. This knowledge gap is particularly important given the rising prevalence of MASLD in younger populations and the need for early intervention to reduce cardiovascular risk.

Our study aims to explore the link between MASLD and carotid plaque progression over a two-year period in a cohort of young adults, taking into account sex and metabolic risk factors. By addressing this gap, our findings could help inform targeted prevention strategies for this high-risk group.

Methods

Patient and Public Involvement

Patients and public were not involved.

Study Population

The research was conducted using data from a health check-up chain data at the Healthcare Management Center of Peking University International Hospital, which provides annual comprehensive health assessments to the population. The study population and data sources for this study are detailed in a prior article.[15] In summary, the study population consisted of individuals who underwent both abdominal and carotid ultrasound examinations between January 2019 to December 2023. Participants were required to be over 18 years of age, had no abnormal carotid status (plaque or stenosis) at baseline and have undergone a minimum of two carotid artery ultrasound examinations to be included in this study. Out of a total of 101,416 individuals, we excluded 16,409 who either lacked baseline abdominal or carotid ultrasound data, had missing information regarding alcohol consumption, or were diagnosed with MASLD with increased alcohol intake. Additionally, 78,409 individuals who had only one carotid ultrasound within the two-year period were also excluded, resulting in a final cohort of 6,598 eligible participants.

The Ethics Committee of Peking University International Hospital approved the research study (ethics number: 2023-KY-0045-01). Since the analyses employed only de-identified data, the requirement for individual consent was waived by the Ethics Committee.

Definitions of Risk Factors

The electronic medical records served as the primary source for the acquisition of all necessary data. Blood samples, obtained following a fasting period of no less than eight hours, were analyzed for lipid profiles (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c], triglycerides [TG]) and glucose levels (fasting plasma glucose [FPG]). Additionally, standard biochemical markers were assessed, including white blood cell count, hemoglobin, platelet count, total lymphocyte count, total neutrophil count, total eosinophil count, total basophil count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, and

estimated glomerular filtration rate (eGFR), all of which were measured using automated platforms. Blood pressure measurements including systolic blood pressure (SBP) and diastolic blood pressure (DBP), along with body mass index (BMI) and waist circumference, were also documented. Trained personnel collected demographic and clinical data in accordance with standardized protocols. Missing values were addressed through regression imputation, utilizing demographic information, smoking and alcohol consumption status, and medication history. Furthermore, given the established association between MASLD and metabolic syndrome (MetS), this study defined five metabolic risk factors in accordance with Chinese guidelines.[16,17]

1. Abdominal obesity: waist > 90 cm or males or > 85 cm for females.
2. High blood pressure: ≥130/85 mmHg, or the use of antihypertensive medications.
3. Hypertgemia: ≥ 1.7 mmol/L, or the use of antilipidemic medications.
4. Low HDL-C: < 1.0mmol /L for males or < 1.3mmol /L for females.
5. Hyperglycemia: fasting blood glucose ≥ 5.6 mmol/L, or a history of type 2 diabetes.

Assessment of MASLD

Utilizing a Doppler ultrasound system, trained sonographers conducted abdominal ultrasonography employing a high-resolution linear array transducer with a frequency range of 3 to 5 MHz. Following an eight-hour fasting period, participants were instructed to assume a supine position on the examination table, with their legs flexed and abdominal muscles relaxed. After taking deep breaths, participants were required to hold their breath for a duration of 3 to 5 seconds prior to the systematic exploration of the liver. This exploration commenced with a sweep of the left lobe of the liver, followed by an oblique sweep from the left subcostal margin. Subsequently, a longitudinal sweep was conducted from the left median paracentral area to the right median paracentral area, followed by an oblique sweep from the right subcostal margin. The examination concluded with an exploration of the right intercostal oblique segment. All ultrasound examinations were conducted in professional physical examination centers affiliated with a high-level hospital, and all sonographers have undergone standardized job training prior to the measurements. Notably, the sonographers were blinded to other clinical data of the participants during the measurements.

The diagnosis of MASLD is based on liver imaging findings that fulfill the diagnostic criteria for diffuse steatotic liver disease. Additionally, it requires the absence of a self-reported history of alcohol consumption exceeding 140 grams per week for men and 70 grams per week for women. Furthermore, it is essential to exclude specific conditions that may contribute to steatotic liver disease, including viral hepatitis, drug-induced liver disease, total parenteral nutrition, hepatolenticular degeneration, and autoimmune liver disease, in accordance with the clinical guidelines.[18] The image manifestations of fatty liver include any one of the following criteria:

1. Near-field echoes are more pronounced in the liver than in the kidneys and spleen, with far-field echoes gradually attenuating.
2. Intrahepatic ductal structures are poorly visualized.
3. The liver is mildly to moderately enlarged with rounded margins.
4. Color Doppler flow imaging shows reduced or barely visible colored intrahepatic flow signals, but the vascular structure remains normal.
5. The echoes of the right liver lobe and transverse septum are unclear.

Assessment of Carotid Plaques

A Doppler ultrasound system (Mindray DC-8S, Mindray, China) was utilized for carotid ultrasonography, conducted by trained sonographers using a high-resolution linear array transducer with a frequency range of 3 to 12 MHz. Participants were instructed to remain in a supine position, with their heads rotated 45° towards the contralateral side of the artery.

The detection of atherosclerotic plaques involved a comprehensive examination of both the proximal and distal walls of the common carotid artery, including the carotid bifurcation, external carotid artery, and internal carotid artery. Atherosclerotic plaques are characterized by focal thickening that encroaches upon the lumen of any segment of the

carotid artery or by a thickness exceeding 1.5 mm, as measured from the intima-lumen interface to the media-adventitia interface. The outcome of our study was defined as the progression of carotid plaque over a two-year period, which was indicated by the emergence of a newly identified carotid plaque among participants who exhibited no abnormal carotid status at baseline.

Statistical Analysis

For data that followed a normal distribution, a two-sided *t*-test was employed for comparative analyses, with results reported as mean ± standard deviation (SD). In cases where the data did not adhere to a normal distribution, the Wilcoxon–Mann–Whitney test was utilized, and results were presented as median with interquartile range. Categorical variables were described as frequencies and percentages, with differences in proportions assessed using either the chi-square test or Fisher's exact test. Additionally, the standardized mean difference (SMD) was employed to compare the characteristics of participants with and without disease progression, in order to mitigate the potential unreliability of p-values that may arise from significant disparities in sample sizes. An absolute SMD greater than 0.2 was considered to indicate a large effect size.

A logistic regression model was employed to access the relationship between baseline MASLD and progression of carotid plaque, with results reported as odds ratios (ORs) accompanied by 95% confidence intervals (CIs). A series of models were implemented to further clarify these associations: the unadjusted mo adjusted model 1, which adjusted for age and sex; model 2, which included additional adjustments for smoking history, alcohol consumption, hypertension, diabetes, dyslipidemia, and chronic kidney disease; and model 3, which further included adjustments for physical examination and laboratory test indicators, such as blood pressure, pulse rate, body mass index, waist circumference, blood lipid and glucose, as well as other relevant laboratory tests. The covariates for the logistic regression model were selected based on similar criteria, including baseline difference, inclusion in previous comparable studies, and expert judgment.

Our methodology involved conducting separate analyses stratified by sex and amount of metabolic risk factors for all previously mentioned analyses. Additionally, we performed subgroup analyses among males based on the presence of the following risk factors: age, BMI, smoking, alcohol consumption, hypertension, diabetes mellitus, and metabolic risk factors. All subgroup analyses were all conducted using a fully adjusted model.

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina). Statistical significance was established at a threshold of $p < 0.05$.

Results

Characteristics of Subjects

The study included a total of 6,589 patients (Figure 1), among whom 2,411 (36.54%) were diagnosed with MASLD, while 4,187 (63.46%) did not have MASLD at baseline. The mean age of the participants was 38.75 ± 7.47 years. Males represented 63.91% of the cohort. The baseline characteristics of the study population are presented in Table 1.

Patients diagnosed with MASLD exhibited a significantly higher prevalence among males (85.94% compared to 51.23%). Additionally, these patients presented with an elevated BMI of 26.87 ± 3.33, in contrast to 22.9 ± 2.86 for the comparison group. Waist circumference measurements were also significantly higher in the MASLD cohort, averaging 91.47 ± 8.49 cm compared to 79.47 ± 8.74 cm. A greater proportion of patients with MASLD reported a history of smoking (31.27% versus 13.95%) alongside a higher prevalence of other comorbidities. Furthermore, individuals with MASLD demonstrated elevated levels of blood pressure, glucose, and lipids, as well as a higher number of metabolic risk factors (see Table 1). Similar characteristics were observed when analyzing males and females separately (refer to Supplementary Table 1).

Associations Between MASLD and Progression of Carotid Plaque

A total of 626 participants (9.49%) were identified as having new-onset carotid plaque over a two-year period. Among these, 338 cases were observed in participants with MASLD, while 288 cases were found in participants without

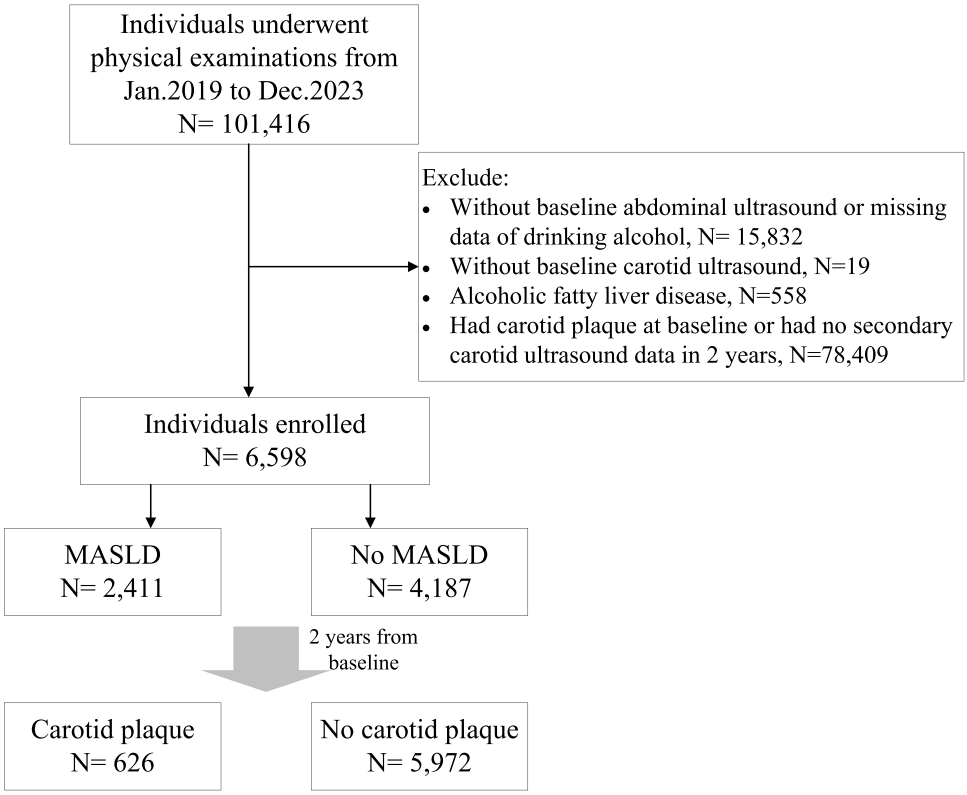

Figure 1 Flowchart of enrollment.

MASLD, accounting for 14.02% and 6.88% of the total number of participants in each group respectively. The incidence rates of carotid plaque were 6.43% (153 out of 2,381) in females and 11.21% (473 out of 4,217) in males, respectively. Participants who exhibited progression of plaque had a significantly higher prevalence of MASLD (53.99% vs 34.71%, SMD = 0.396). Additionally, these individuals were more likely to be male, older, and to have higher BMI and waist circumference, as well as elevated blood pressure and lipid levels. They also demonstrated a greater prevalence of smoking, hypertension, and other metabolic risk factors. Notably, both females and males exhibited similar characteristics (see Table 1 and Supplementary Table 2).

Statistically significant positive associations were identified in unadjusted logistic regression models for both the overall population and each sex, as presented in Table 2. However, upon adjusting for all covariates in the fully adjusted model (adjusted model 3), statistically significant odds ratios were not observed for the overall population (OR=1.24, 95% CI: 0.99–1.55) or for males (OR=1.09, 95% CI: 0.85–1.4). In contrast, the positive association remained robust among females, indicating that women with MASLD exhibited a higher risk of disease progression in both unadjusted and adjusted models. In the fully adjusted model, the odds ratio for females was 2.19 (95% CI: 1.28–3.72). Furthermore, this positive association was also consistent among participants without metabolic risk factors, yielding an odds ratio of 1.67 (95% CI: 1.01–2.76). The association was marginally significant among individuals with only one risk factor but was no longer significant among those with two or more risk factors.

Association Between MASLD and Progression of Carotid Plaque in Subgroups

No significant associations were identified among all male subgroups. However, positive associations remained statistically significant among females aged over 40 years who did not engage in smoking or alcohol consumption, were classified as overweight (BMI ≥ 24), and had no history of hypertension or diabetes. Notably, significant associations were observed in females without any metabolic risk factors (OR: 3.35, 95% CI: 1.15–9.78) as well as in those with three or more metabolic risk factors (OR: 22.85, 95% CI: 1.76–296.3) (see Figure 2).

Table 1 Characteristics of All Participants with and without MASLD

Characteristics	Overall N=6598	MASLD N=2411	Non-MASLD N=4187	P value
Progress of carotid plaque	626(9.49)	338(14.02)	288(6.88)	<0.01*
Age, years	38.75±7.47	39.52±7.39	38.3±7.49	<0.01*
Sex				
Male	4217(63.91)	2072(85.94)	2145(51.23)	<0.01*
Female	2381(36.09)	339(14.06)	2042(48.77)	
BMI, kg/m^2	24.35±3.59	26.87±3.33	22.9±2.86	<0.01*
Smoking history	1338(20.28)	754(31.27)	584(13.95)	<0.01*
Alcohol consumption	910(13.79)	340(14.1)	570(13.61)	0.58
Disease History				
Hypertension	497(7.53)	312(12.94)	185(4.42)	<0.01*
Diabetes	129(1.96)	76(3.15)	53(1.27)	<0.01*
Dyslipidemia	149(2.26)	98(4.06)	51(1.22)	<0.01*
Coronary heart disease	34(0.52)	19(0.79)	15(0.36)	0.02*
Physical and lab examination				
SBP, mmHg	116.97±14.28	122.86±13.73	113.59±13.47	<0.01*
DBP, mmHg	71.13±10.83	75.7±10.8	68.5±9.93	<0.01*
Waist circumference,cm	83.85±10.4	91.47±8.49	79.47±8.74	<0.01*
FPG, mmol/L	5.02±0.95	5.3±1.31	4.85±0.61	<0.01*
TC, mmol/L	4.63±0.83	4.84±0.87	4.51±0.79	<0.01*
TG, mmol/L	1.13(0.76, 1.76)	1.75(1.23, 2.53)	0.9(0.65, 1.28)	<0.01*
HDL-C, mmol/L	1.26±0.3	1.09±0.21	1.35±0.3	<0.01*
LDL-C, mmol/L	2.73±0.7	2.92±0.71	2.62±0.67	<0.01*
White blood cell count, 10^9/L	5.73±1.4	6.24±1.44	5.43±1.3	<0.01*
Hemoglobin, g/L	146.21±16.04	153.95±12.52	141.75±16.15	<0.01*
Platelet count, 10^9/L	241.68±53.66	246.75±53.61	238.76±53.48	<0.01*
Total lymphocyte count, 10^9/L	1.84±0.49	1.98±0.51	1.76±0.46	<0.01*
Total neutrophil count, 10^9/L	3.39±1.09	3.7±1.12	3.21±1.03	<0.01*
Total eosinophil count, 10^9/L	0.09(0.05, 0.16)	0.11(0.07, 0.18)	0.08(0.05, 0.14)	<0.01*
Total basophil count, 10^9/L	0.03(0.02, 0.05)	0.04(0.03, 0.05)	0.03(0.02, 0.04)	<0.01*
ALT,U/L	19(13, 29)	29(20, 43)	15(11, 21)	<0.01*
AST,U/L	22.29±10.42	25.98±11.95	20.17±8.75	<0.01*
Albumin,g/L	45.53±2.32	46.06±2.23	45.22±2.31	<0.01*
Total bilirubin, umol/L	14.18±5.85	14.39±5.87	14.06±5.84	0.03*
eGRF	101.65±15.74	100.99±15.69	102.03±15.77	0.01*
eGRF<60	8(0.12)	3(0.12)	5(0.12)	0.96
Metabolic risk factors				
Abdominal obesity	1777(26.93)	1273(52.8)	504(12.04)	<0.01*
High blood pressure	1331(20.17)	775(32.14)	556(13.28)	<0.01*
Hypertgemia	1755(26.6)	1264(52.43)	491(11.73)	<0.01*
Low HDL-C	1952(29.58)	1011(41.93)	941(22.47)	<0.01*
Hyperglycemia	724(10.97)	468(19.41)	256(6.11)	<0.01*
Amount of metabolic risk factors				
0	2635(39.94)	316(13.11)	2319(55.39)	<0.01*
1	1781(26.99)	565(23.43)	1216(29.04)	
2	1175(17.81)	703(29.16)	472(11.27)	
3	682(10.34)	545(22.6)	137(3.27)	
4	263(3.99)	225(9.33)	38(0.91)	
5	62(0.94)	57(2.36)	5(0.12)	

Note: * P value<0.05.

Abbreviations: FPG, fasting plasma glucose; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 2 Association Between MASLD and Progression of Carotid Plaque Based on Logistic Model

	Unadjusted Model			Adjusted Model 1			Adjusted Model 2			Adjusted Model 3		
	OR (95% CI)	**p value**	**p for Interaction**	**OR (95% CI)**	**p value**	**p for Interaction**	**OR (95% CI)**	**p value**	**p for Interaction**	**OR (95% CI)**	**p value**	**p for Interaction**
Overall	2.21(1.87,2.61)	<0.01*		1.79(1.5,2.15)	<0.01*		1.72(1.43,2.07)	<0.01*		1.24(0.99,1.55)	0.06	
Sex			0.01*			0.50			0.35			0.56
Female	3.04(2.12,4.37)	<0.01*		1.9(1.28,2.81)	<0.01*		1.99(1.33,2.97)	<0.01*		2.19(1.28,3.72)	<0.01*	
Male	1.74(1.43,2.12)	<0.01*		1.73(1.42,2.12)	<0.01*		1.63(1.33,2)	<0.01*		1.09(0.85,1.4)	0.48	
Amount of metabolic risk factors			0.23			0.72			0.64			0.68
0	2.09(1.35,3.23)	<0.01*		1.88(1.18,3)	<0.01*		1.87(1.17,3)	0.01		1.67(1.01,2.76)	0.05*	
1	1.67(1.22,2.29)	<0.01*		1.55(1.1,2.18)	0.01		1.55(1.1,2.18)	0.01		1.43(0.97,2.1)	0.07	
2	1.05(0.74,1.5)	0.77		1.02(0.7,1.48)	0.907		1(0.69,1.45)	0.98		0.93(0.62,1.4)	0.72	
≥3	1.36(0.85,2.17)	0.20		1.51(0.93,2.45)	0.096		1.55(0.95,2.55)	0.08		1.48(0.88,2.48)	0.14	

Notes: * p value<0.05. Adjusted model 1: adjusted for age and sex; Model 2: further adjusted for history of smoking, alcohol, hypertension, DM, and hyperlipidemia; Model 3: further adjusted for physical exam or lab test indicators.

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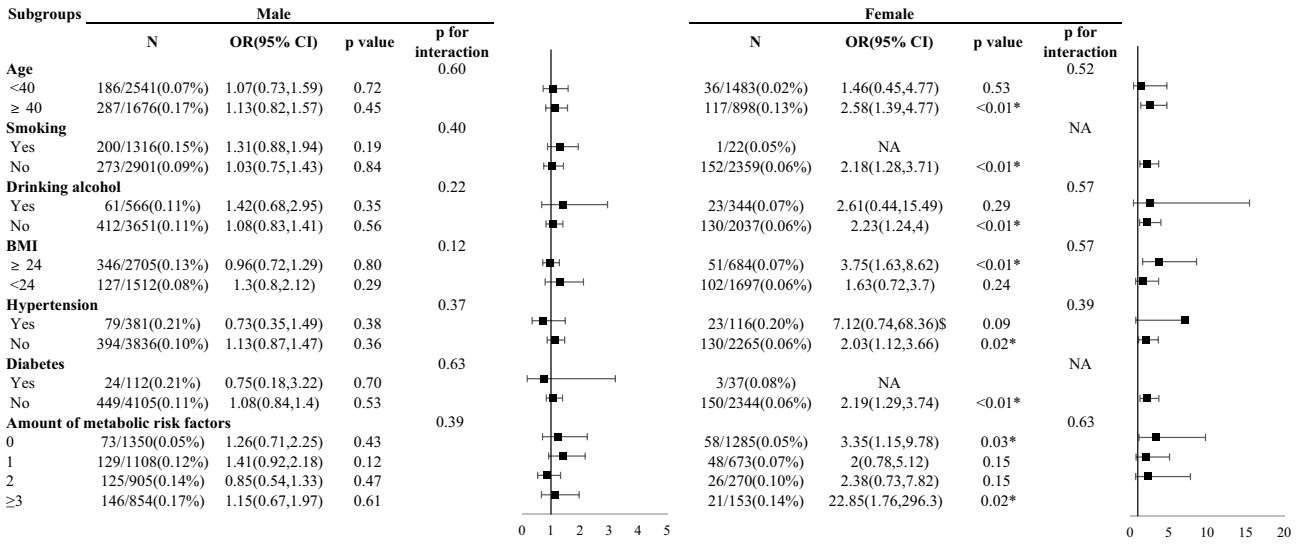

Figure 2 Association between MASLD and progression of carotid plaque among subgroups. * p value<0.05. Based on full adjusted logistic mo $not shown in plot since of too wide range of confident interval.

Discussion

Our study identified a significant association between MASLD and the progression of carotid plaque over a two-year period in early middle-aged adults. Specifically, individuals with MASLD were more likely to develop new carotid plaques compared to those without MASLD, with the strongest effects observed in females and those without metabolic risk factors. These findings suggest that MASLD may serve as an early marker of subclinical atherosclerosis, even in the absence of traditional metabolic abnormalities.

The observed association between MASLD and accelerated short-term carotid plaque progression supports existing evidence that MASLD exerts systemic vasculopathic effects beyond its hepatic manifestations. This relationship persists independently of traditional cardiovascular risk factors, suggesting that MASLD may serve as an independent atherogenic factor.[2] Kang et al[18] demonstrated through longitudinal analysis that MASLD independently predicted increased carotid intima-media thickness (IMT) progression in non-diabetic adults, with this association remaining significant after adjusting for metabolic syndrome components. Complementary findings by Pacifico et al in pediatric populations revealed that obese children with MASLD exhibited greater carotid IMT values compared to BMI-matched controls without hepatic steatosis,[13] highlighting the disease's early atherogenic potential across age spectra. In addition, in our study, when adjusting for all covariates in the full model, statistically significant odds ratios were not observed for the overall population. Previous study has shown that proliferation and dysfunction of the vasa vasorum can be a very early marker of plaque development,[19] and there is currently no strong evidence that MASLD is associated with vasa vasorum dysfunction, which may partly explain the limited predictive value of MASLD in fully adjusted models. Our investigation also found that traditional cardiovascular risk factors (eg, hypertension, dyslipidemia, diabetes) may play a more dominant role in the development of atherosclerosis compared to MASLD, and advances this understanding by quantifying plaque progression rates, demonstrating that young adults (mean age 38.75 ± 7.47 years), especially female with MASLD, experience carotid plaque accumulation compared to non-MASLD participants over a 24-month observation period.

It is important to acknowledge that the MASLD group in our study also exhibited a higher prevalence of conventional cardiovascular risk factors, including increased glucose levels, higher triglycerides, altered lipid profiles, and increased smoking rates. These established risk factors are well-known contributors to atherogenic plaque formation, and their presence in the MASLD cohort suggests that the observed plaque progression is likely a result of the collective burden of these traditional risks, rather than MASLD in isolation being the direct sole cause.[2] Our study's fully adjusted models, which attenuated the overall association, support this notion, indicating that while MASLD is a strong indicator of an at-risk metabolic state, these co-occurring traditional risk factors are significant drivers of atherosclerosis in the general population.

A noteworthy finding was the sex difference in the relationship between MASLD and carotid plaque progression. The association remained significant in females but was not statistically significant in males after full adjustment, suggesting that MASLD may confer a greater cardiovascular risk in women. This disparity may be due to metabolic and hormonal differences influencing atherosclerosis risk. Estrogen has known protective effects against atherosclerosis by improving lipid profiles, reducing inflammation, and enhancing endothelial function. However, in women with MASLD—especially postmenopausal or metabolically unhealthy individuals—these protective effects may be diminished, leading to increased vascular risk. Supporting this, Xue et al also reported a stronger association between MASLD and carotid plaque in lean females,[20] potentially due to differences in fat distribution or estrogen-related mechanisms. Behavioral and sociocultural factors may also contribute. While male sex is a well-established risk factor for MASLD, in the Chinese context, gendered lifestyle patterns could modulate disease risk. For example, men are more likely to participate in social dining and alcohol consumption, behaviors that increase the risk of hepatic steatosis and metabolic comorbidities. Taken together, these findings highlight the importance of considering sex-specific physiological and behavioral factors when assessing the cardiovascular implications of MASLD. Future research should aim to elucidate the hormonal pathways and behavioral mediators that may account for these disparities. A recent study further emphasizes the need for sex-specific strategies in the management of MASLD, given the clear differences in disease progression and cardiovascular outcomes between men and women.[21]

Our study also found the significant association between MASLD and carotid plaque progression in individuals without metabolic risk factors. This suggests that MASLD may signal early metabolic dysfunction before the onset of overt metabolic syndrome. Similar findings were reported that MASLD was linked to carotid atherosclerosis even in the absence of metabolic syndrome, implying that hepatic steatosis itself may contribute to vascular damage through pathways independent of traditional risk factors.[17] These findings highlight the importance of screening for MASLD in young adults, as it may help identify individuals at risk of early atherosclerosis before other metabolic abnormalities emerge. This advances current knowledge by challenging the assumption that MASLD-related cardiovascular risk is solely a consequence of accompanying metabolic conditions like obesity or diabetes, thus identifying a new target population for early intervention.

The exact cause of MASLD in individuals without traditional metabolic syndrome parameters is multifactorial and a subject of ongoing research, but several mechanisms are implicated. Key factors often include specific genetic predispositions, subtle but critical defects in adipose tissue function leading to excess fatty acid release (adiposopathy), high consumption of dietary sugars like fructose, and perturbations in the gut microbiome. Even with a normal BMI, these individuals may have increased visceral adiposity, which contributes to a pro-inflammatory state and insulin resistance at a molecular level not captured by standard clinical parameters. This emphasizes that "metabolically healthy" status based on simple clinical cutoffs may mask underlying, subtle metabolic derangements at the cellular level that drive both hepatic steatosis and vascular damage. The primary intervention for managing MASLD and reducing cardiovascular risk remains weight loss through lifestyle modification; however, emerging evidence highlights complex physiological mechanisms beyond simple caloric restriction. A critical review of the literature on bariatric surgery emphasizes that these changes in GI hormone secretion are likely necessary for the long-term success of the procedure, independent of the physical restriction of the stomach size, offering valuable insights into potential therapeutic targets for MASLD management.[22] This underscores the importance of targeting these hormonal pathways in future therapeutic strategies, such as with GLP-1 receptor agonists, which have demonstrated promising results in reducing liver fat and improving liver function markers.

Our study has several strengths. First, by utilizing prospective data to define new-onset carotid plaque, we provide a clearer temporal relationship between MASLD and atherosclerosis progression in a large cohort. Second, we focused on a young adult population—an underrepresented group in cardiovascular research—and demonstrated that atherosclerotic changes can occur rapidly in this demographic. By highlighting the short-term cardiovascular impact of MASLD, our study reinforces the need for early intervention to mitigate long-term risks. Third, a major strength is the emphasis placed on sex-specific and metabolic subtype analyses, revealing novel insights into the differential risk conferred by MASLD in females and metabolically healthy individuals. Finally, by carefully adjusting for a wide range of covariates, we have provided robust evidence that even in early middle age, MASLD is a critical factor for subclinical atherosclerosis, reinforcing the urgent need for early screening and intervention to mitigate long-term cardiovascular risks.

However, our study has limitations. First, as a single-center study based on health check-up data, our findings may not be fully generalizable. Second, as this study adopted a retrospective data collection method, some variables were limited, such as lacking information on diet, physical activity, and socioeconomic status. This uncollected information might contain unmeasured confounding. Besides, this study was also unable to design the inter-rater agreement of ultrasound measurement, although we are very confident in the quality of the ultrasonic data because all measurements are conducted by professionally trained and licensed doctors. Third, MASLD was diagnosed using ultrasound rather than MRI or liver biopsy, which may underestimate disease severity. Nevertheless, ultrasound remains a widely accepted non-invasive diagnostic tool for MASLD in clinical practice, as supported by previous studies. Fourth, the relatively short two-year follow-up period may limit the ability to detect meaningful atherosclerotic progression, particularly in a younger population where changes are typically gradual. Fourth, our study demonstrates an association between MASLD and atherogenic plaque formation; we have not investigated causality. Although we adjusted for traditional risk factors such as smoking status, blood glucose and lipid levels in the statistical analysis, the higher baseline smoking rate and the proportion of metabolic abnormalities in the MASLD group may still have residual confounding effects on the observed associations. Furthermore, this study failed to obtain and adjust for genetic susceptibility factors, which may simultaneously affect the risk of MASLD and atherosclerosis, thereby potentially confounding the observed associations. Future research that combines genetic data will help clarify this issue. As atherosclerosis is a chronic and slowly evolving process, longer-term follow-up would provide more robust evidence and strengthen the validity of these findings. Finally, in some female subgroups, such as those with $\geq$3 metabolic risk factors, very high odds ratios were observed, accompanied by wide confidence intervals. These imprecise estimates suggest potential model instability due to small sample sizes and warrant cautious interpretation. Future studies with larger samples and extended follow-up are needed to confirm these subgroup findings and further clarify the sex-specific cardiovascular risks associated with MASLD.

In conclusion, our findings indicate that MASLD is linked to an increased risk of carotid plaque progression in young adults, especially in females and those without metabolic risk factors. These results suggest that MASLD may serve as an early marker of subclinical atherosclerosis, emphasizing the importance of targeted screening and preventive measures for this population. Future research should further investigate the mechanisms connecting MASLD to atherosclerosis and evaluate whether interventions addressing MASLD can help mitigate cardiovascular risk.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy considerations and the protection of individual rights, but are available from the corresponding author on reasonable request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Due to the retrospective data collection of the study, ethics committee at Peking University International Hospital waived the need of obtaining informed consent.

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Author Contributions

Wenjing Xiao and Xinghe Sun are co-first authors. All authors made a significant contribution to the work reported. Jihong Zhu and Xiaohui Liu took responsibility in the conceptualization, study methodology and project administration. Wenjing Xiao and Xinghe Sun took responsibility in investigation, data curation, formal analysis and validation,

visualization and interpretation. Hui Lv took responsibility in investigation and data curation. All authors contributed to writing – original draft and writing – review and editing the article; have agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication; and agree to take responsibility and be accountable for the contents of the article.

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Disclosure

The authors declared no relevant conflict of interest.

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